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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,652	08/07/2001	Ronald A. Laskey	620-161	9664

7590 02/25/2003

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,652	LASKEY ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-100 and 105-109* is/are rejected.

7)☒ Claim(s) *101-104* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/175,947* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

In view of applicant's arguments (Paper No. 10), the restriction requirement/species election mailed 11-05-02 (Paper No. 9) is withdrawn.

Claims 88-109 are pending and are currently under consideration.

Priority

A review of the parent application, provisional applications, and foreign applications reveals that the scope of enablement and written description drawn specifically to determining the presence or absence of dysplastic or neoplastic cells in a test sample by determining the amount and or pattern of antibody binding to Minichromosome Maintenance protein 2 (**MCM2**) was not disclosed until May 15, 1998 in the United Kingdom (UK 9810560.4, 05/15/1998). If applicant disagrees with any rejection of claims 88-109 set forth in this office action based on the examiner's establishment of a priority date of May 15, 1998 for the instant claims in application serial number 09/922,652, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 88-100, 105 are rejected under 35 U.S.C. 102(b) as being anticipated by Werness *et al.* Laboratory Investigation, Vol. 76, No.1, page 185A, March 1997.

The specification teaches (page 15) that the Human MCM2 sequence is **disclosed** in Todorov *et al.* 1994, J.Cell Science, 107, 253-265, GenBank Acc. No. X67334. However, a review of GenBank Accession No. X67334 revealed a polynucleotide sequence encoding the amino acids of a protein referred to as "BM28"- which appears to be the human form of MCM2. Thus, absent evidence to the contrary and absence a specific sequence identifier, the recitation of MCM2 in the claims is considered to be the same as any reference to BM28 or BM28/CDCL1.

Werness *et al.* teach a method of determining the presence or absence of dysplastic or neoplastic cells in a test sample from an individual (i.e., the samples were from primary human tumors and normal tissues) comprising contacting the test sample with an antibody directed against BM28/hMCM2 (see title) and determining the amount and or pattern of said antibody to the test sample whereby an increase in said amount and or a difference in said pattern if detected for the test sample compared with normal is indicative of presence of neoplastic cells in the test sample. Werness *et al.* teach that "tissue sections reacted with anti-BM28 gave strong nuclear signals in normal proliferating cells" and "tumors exhibited more intense positive staining of most nuclei"; the later reading **both** on wherein binding of the antibody to hMCM2 in the test sample is indicative of the presence of neoplastic cells (Claim 89) or wherein a difference in pattern of binding (i.e. more intense positive staining) of the antibody to said test sample compared with normal is indicative of the presence of neoplastic cells in said test sample (Claim 90). Werness *et al.* also teach that "frozen, unfixed tissue" from 72 tumors and 22 normal tissues

were analyzed. Accordingly, such tissues were not formalin fixed or paraffin embedded and were not the subject of antigen retrieval or pressure cooking/autoclaving (Claims 92-94). Also, since the tissues tested were from a multitude of primary human tumors and normal tissues, the art reads on the screening of a population of individuals (Claim 105).

Furthermore, although the abstract does not teach the *specific* type of tumor tissues tested, the art teaches the exact same method as that which is claimed: analyzing the amount or pattern of hMCM2 protein in tumor tissues versus normal tissues, contacting the tissues with an antibody which binds to hMCM2, using frozen, unfixed tissues. Thus, all things being equal, inherently, of the 72 tumors tested from the tissue sections included in the method of Werness *et al.*, one of ordinary skill in the art of oncology and histology would have a reasonable expectation that samples from either lung tissue, breast tissue, colon tissue, prostate tissue, stomach tissue, skin tissue, oesophagus, and or bladder tissue were included in the tissue sections of Werness *et al.*

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 88-100, 105 are further rejected under 35 U.S.C. 102(a) as being anticpated by Todorov *et al.* (Laboratory Investigation, January 1998, Vol. 78, No. 1, pages 73-78, IDS).

The specification teaches (page 15) that the Human MCM2 sequence is **disclosed** in Todorov *et al.* 1994, J.Cell Science, 107, 253-265, GenBank Acc. No. X67334. However, a review of GenBank Accession No. X67334 revealed a polynucleotide sequence encoding the amino acids of a protein referred to as "BM28"- which appears to be the human form of MCM2.

Thus, absent evidence to the contrary and absence a specific sequence identifier, the recitation of MCM2 in the claims is considered to be the same as any reference to BM28 or BM28/CDCL1.

Todorov *et al.* teach a method of determining the presence or absence of dysplastic or neoplastic cells in a test sample from an individual (i.e., the samples were from primary human tumors and normal tissues) comprising contacting the test sample with an antibody directed against BM28/hMCM2 (see title) and determining the amount and or pattern of said antibody to the test sample whereby an increase in said amount and or a difference in said pattern if detected for the test sample compared with normal is indicative of presence of neoplastic cells in the test sample. Tudorov *et al.* teach that in frozen tissue sections, not paraffin embedded, the tissues showed a strong reaction of the anti-HsMCM2 antibody with almost all (70 of 72) tumor samples (page 73, 2nd column) compared to their normal counterpart tissue. Tudorov *et al.* further teach a difference in pattern of binding (i.e. more intense nuclear positive staining) of the antibody to said test sample compared with normal is indicative of the presence of neoplastic cells in said test sample (page 74, 2nd column). Tudorov *et al.* further teach that the tumor samples were derived from tissue selected from the group consisting of lung, breast, and colon (Table 1, page 74). Also, since the tissues tested were from a multitude of primary human tumors and normal tissues, the art reads on the screening of a population of individuals.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 88-100, and 105-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Todorov *et al.* (Laboratory Investigation, January 1998, Vol. 78, No. 1, pages 73-78, IDS) in further view of Murphy *et al.* (Clinical Oncology, American Cancer Society, 2nd edition, 1995, pages 553-554).

Todorov *et al.* teach (as set forth above) the testing of 44 adenocarcinomas (Table 1, page 74) including tissue from the endometrium and ovaries.

Todorov *et al.* do not specifically include determining the presence or absence of dysplastic or neoplastic cells in a test *cervical* sample comprising contacting the cervical sample with an antibody against MCM2.

Murphy *et al.* teach (page 553) that most cervical cancers develop from the transformation zone, whereby columnar epithelium undergoes metaplasia to become squamous epithelium. Murphy *et al.* further teach that adenocarcinoma of the cervix accounts for 5% to 20% of cervical carcinomas and that epidemiologically, cervical adenocarcinomas affects the same patient population as endometrial or ovarian carcinoma.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the testing of cervical neoplasia and or a test cervical smear in the method as set forth by Todorov *et al.* because Todorov *et al.* successfully identify the presence of neoplastic cells comprising contacting an antibody against HsMCM2 in a variety of different tumors (i.e. breast, colon, lung, kidney, skeletal muscle) versus their normal counterpart tissues. Further, Todorov *et al.* teach that certain gynecological tumor tissues (i.e, ovary and endometrium) also were positive for the expression of HsMCM2 (Table 1, page 74). Further, one would have been motivated to include dysplastic or neoplastic tissue from the cervix because Murphy *et al.* teach that adenocarcinoma of the cervix accounts for 5% to 20% of cervical carcinomas and that epidemiologically, cervical adenocarcinomas affects the same patient population as endometrial or ovarian carcinoma. Thus, since Todorov *et al.* successfully differentiate a multitude of various tumor samples from their normal counterparts by analyzing the expression of HsMCM2, and since HsMCM2 was also present in certain gynecological tumor samples, one of ordinary skill in the art would have a reasonable expectation of success that HsMCM2 would also be expressed in neoplastic or dysplastic cervical samples and or a cervical smear compared to normal cervical samples.

Claims 101-104 are objected to as being dependent from a rejected base claim.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
February 24, 2003